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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

SCHNEIDER et al

Atty. Ref.: 1201-45

Serial No. 08/893,371

Group: 1211

Filed: July 15, 1997

Examiner: Hollinden

For: STABLE MICROBUBBLES SUSPENSIONS INJECTABLE INTO LIVING ORGANISMS

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October 27, 1997

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

OCT 28 1997

INFORMATION DISCLOSURE STATEMENT

Sir:

Attention is invited to the documents listed on the attached PTO-1449 which may be of interest in this application. Several of these are identified and discussed in the specification of this application. Copies of these documents are in the file of application Serial No. 08/855,055 filed May 13, 1977 now pending in Art Unit 1211.

Official citation and consideration of all the attached documents is requested. Please return to the undersigned a copy of the attached PTO-1449 with the examiner's initials in the left column [MPEP §609] with the next communication.

The filing of an Information Disclosure Statement shall not be construed as a representation that a search has been made [37 C.F.R. § 1.97(g)], an admission that the information cited is, or is considered to be, material to patentability or that no other material information exists.

Further, the filing of an Information Disclosure Statement shall not be construed as an admission against interest in any manner [Commissioner's Notice of January 9, 1992, 1135 O.G. 12-25 at 25].

Respectfully submitted,

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US 4,265,251 (Tickner) - Discloses a method of measuring the blood pressure of a patient by administering a solid microbubble precursor and maintaining it in the blood for sufficient time to dissolve and liberate a number of gas microbubbles in the range of 0.5 - 325 microns. Characteristics of the sonic signals of the microbubbles, representative of the pressure in the blood, are measured and the pressure in the blood stream determined as a function of time. The gases mentioned are nitrogen, oxygen, argon, air freon, etc. but only carbon dioxide is exemplified. Col. 3, lines 65-68 refers to microbubbles with diameters between 150-1 μm preferably 25 μm however the document provides no teaching regarding a method of manufacture of microbubbles with diameters between 0.5 and 10 μm required for imaging of the left heart.

US 4,276,885 (Tickner et al.) - Discloses a method of ultrasonic imaging by injecting an aqueous suspension of nitrogen containing microbubbles into the blood stream of patients. The microbubbles have a coalescence resistant surface membrane from a non-toxic and non-antigenic material (gelatin). Upon injection the membrane material gradually dissolves releasing nitrogen microbubbles increasing the relative contrast between the liquid and its surrounding. The microbubbles are of 0.5-300 microns in diameter. The only example illustrates microbubbles with 38, 80 and 140 μm in size. No teaching regarding a method of making 0.5-10 μm microbubbles required for left heart imaging is provided.

US 4,316,391 (Tickner et al.) - Discloses a method of measuring blood flow rate in a cardiovascular system using ultrasound. The method consists of injecting a substance which provides a plurality of microbubbles into the blood stream of a living being and detecting backscater of ultrasonic pulses.

US 4,466,442 (Hilmann et al.) - Discloses an ultrasonic contrast agent comprising gas microbubbles stabilized by a liquid mixture of 0.01-10% by wt. of a surfactants (e.g. lecithin, glycerol, polyethylene glycol, cholesterol, polyoxyethylene-polyoxypropylene polymer, etc.) in an aqueous carrier liquid and 0.5-50% of a viscosity increasing substance(s) such as cyclodextrin, mono-, di- or trisaccharide, polyol or (in)organic salt, galactose, glucose or alpha-cyclodextrin, etc. and an aqueous carrier liquid, the two mixtures being separate or combined. The bubbles are introduced (under sterile conditions) by various means (e.g. by repeated pumping in and out of a syringe) under sterile conditions.

US 4,572,203 (Feinstein) - Discloses a method of ultrasonic imaging of patients by injecting biodegradable metal-containing microparticles and scanning the patient.

US 4,657,756 (Rasor et al.) - Discloses a sterile injectable fluid composition capable of generating microbubbles comprising a suspension of a non-toxic, physiologically acceptable particulate solid material, soluble in blood. The particles (dextrose, galactose, maltose or NaCl) have an average size of 1-250 microns and are aggregates having gas-filled voids. The fluid is aqueous and has a viscosity greater than water.

US 4,681,119 (Rasor et al.) - Discloses a method of ultrasonic imaging by injecting into patients an aqueous composition capable of generating microbubbles comprising a suspension of a non-toxic, physiologically acceptable particulate solid material, soluble in blood. The particles have gas-filled voids, communicating with the surface, and many nuclei for microbubble formation.

US 4,684 479 (D'Arrigo) - Discloses a composition for making stable gas-in-liquid emulsions useful in medicine, explosives, etc. comprising a surfactant mixture and a liquid carrier. Emulsions comprise a mixture of fatty acid esters such as a glycol monoester of a saturated 10-18C carboxylic acid; (b) a sterol-aromatic ester; (c) a sterol, terpene, bile acid, etc; (d) a sterol ester of aliphatic acids or a sugar acid, a saponin; or a sapogenin; and (e) glycerol. Stable microbubbles are formed in an aqueous or oil-based medium by shaking in the presence of gas. The surfactant mixture can be in powder form. One of the disclosed uses is in echo cardiography.

US 4,718,433 (Feinstein) - Discloses a method of ultrasonic imaging of myocardial tissue and perfusion or blood flow comprising injecting microbubbles into a mammal and ultrasonically scanning the patient. The method is carried out using a contrast agent obtained by sonication of an aqueous protein solution to partially denature the protein which stabilizes air microbubbles.

US 4,774,958 (Feinstein) - Discloses an ultrasonic imaging agent comprising a dispersion of microbubbles stabilized by the denatured protein in an aqueous solution. Preferably the protein is albumin. The microbubbles are biocompatible or biodegradable and are small enough to pass through capillary beds.

US 4,832,941 (Berwing et al.) - Discloses an ultrasonic contrast medium comprising a polysaccharide or polypeptide, (e.g. gelatin) (1-5 wt.%), vegetable oil(s) (1-10 wt.%) (e.g. soya), a non-toxic Fe (II) salt, (0.01-0.05 wt.%); and opt. a sugar alcohol (0-1 wt.%), phospholipids (0-5 wt.%), glycerol (0-2 wt.%) and preservatives; and air, nitrogen or inert gas bubbles.

US 4,844,882 (Widder et al.) - Discloses an ultrasonic imaging agent comprising an aqueous parenteral medium containing a dispersion of gas filled microspheres. The gas microbubbles are enclosed by solid walls formed from heat-insolubilized biocompatible material (albumin). The imaging agent has a concentration above lxlo8 microspheres per milliliter.

US 4,900,540 (Ryan) - Discloses phospholipid liposomes as an ultrasound contrast medium. The liposomes comprise an outer phospholipid layer enclosing a gas precursor from aqueous NaHCO3 and aminomalonate in an amount effective to form a gas under physiological pH conditions. The liposomes can be unilamellar or multilamellar and are prepared using conventional methods.

US 4,957,656 (Cerny et al.) - Discloses an imaging agent for diagnostic use comprising sonicating an aqueous solution of human serum albumin to form minute gas-microspheres. The agent is made by heating of a solution of albumin to temperature of denaturation in the presence of air and forming microspheres of less than 10 microns diameter.

US 5,088,499 (Unger) - Discloses a contrast agent for ultrasonic imaging comprising either (a) an ionophore containing liposome encapsulating a pH activated gaseous precursor; or (b) a liposome encapsulating a photoactivated gaseous precursor; or (c) a liposome encapsulating a temperature activated gaseous precursor; or (d) liposomes containing introduced gas; or (e) a liposome encapsulating a solid or liquid contrast enhancing agent.

US 5,137,928 (Erbel et al.) - Discloses ultrasonic contrast agents comprising a suspension of porous microparticles made of a polyaminodicarboxylic acid in an aqueous carrier. The pores of the microparticles containing gas selected from air, 02, N2, H2, C02, He, Ne, Ar, Kr, etc. The amino acids are alpha and/or beta-linked.

US 5,141,738 (Rasor et al.) - Discloses an injectable contrast medium for ultrasonic diagnosis comprising microparticles of mixture of lipophilic surfactants, (e.g. lecithin, polyoxyethylene fatty acid ester, polyoxyethylated castor oil, polyoxyethylated sorbitan fatty acid ester, glycerol polyethylene glycol oxystearate, cholesterol, etc.), and a non-surfactant water-soluble solid (e.g. organic or inorganic salt) and gas microbubbles. Preferred medium contains 0.01-5% wt. of palmitic acid and 95-99.99 wt.% galactose in below 10 micron particles, which may be aggregated.

US 5,147,631 (Glajch et. al.) - Discloses an ultrasound contrast agent comprising a carrier liquid and porous particles containing an entrapped gas. The particles comprise a monomeric or polymeric inorganic material (e.g. borates, aluminas, carbonates, bicarbonates, silicates, aluminosilicates and phosphates). Preferred gas is air, 02, N2, H2, C02, He, Ne, Ar, CF4 or C2F6. The agent is useful for diagnostic ultrasound imaging of cardiovascular or gastrointestinal systems.

EP-A-0 122 624 (Hilmann et al.) - Discloses that the gas microbubble stabilizing effect of sugars, sugar alcohols and salts may be improved by addition of surfactants. [= ZA 84/2801; CA 1,239,092][1]

EP-A-0 131 540 (Rasor et al.) - Discloses an agent containing microparticles of maltose, dextrose, lactose or galactose and gas bubbles in a liquid carrier (water), a physiological electrolyte solution such as 0.91. NaCl soln, Ringer solution or tyrode solution or an aqueous solution of matose, dextrose, lactose or galactose. The agent is suitable for imaging of heart and veins.

EP-A-0 327 490 (Stein et al.) - Discloses an ultrasonic contrast agent comprising microparticles made of (a) amylose or (b) a synthetic, biodegradable polymer, plus a gas and/or organic liquid of boiling point below 60oC. The particles are made of cyclodextrins; polyesters of hydroxycarboxylic acids, poly(alkyl cyanoacrylate, etc. Typical gas/liquid components are 1,1-dichloroethylene, furan, Et2O, MeBr, pentane, air, N2, C02, propane, etc. The microparticles are useful for diagnosis and therapy. [= AU 3051/89; U.S. 5,425,366]

EP-A-0 357 163 Albayrak et al. - Discloses ultrasonic, X-ray or NMR contrast agents comprising host-guest complexes of cavitate or clathrate type in which the host is capable of dissolving in liquid media to release the guest. Exemplified hosts are tri-o-thymotide, dianin (4-(4-hydroxyphenyl-2,2,2-trimethylchroman), hydroquinone, urea and thiourea. Exemplified guests include MeBr, ethylene oxide, SF6, 1-5C alkanes, C02, cyclopropane, N2 and inert gases. Complexes in which the guest in a gas dissolve in suitable liquid media to form free gas bubbles serving as ultrasonic contrast agents. [= AU 40651/89]

[1] = indicates a related document in English, not necessarily an equivalent or patent family member

EP-A-0 441 468 (Rossling et al.) - Discloses a biodegradable polymer microparticles formed from polymerizable aldehydes, optionally together with (a) copolymerisable additives, (b) surfactants, (c) gases and/or volatile liquids in free or bound form, (d) coupling agents, and/or (e) diagnostically or therapeutically effective components. The microparticles are porous and are hence useful as ultrasonic contrast agents for imaging the blood stream, body cavities, heart or other organs. Among gases which may fill the pores of the particles are ammonia, air, oxygen, nitrogen, SF6, inert gases, hydrocarbons, dibromodifluoromethane, etc. [= U.S. 5,501,863; AU 70982/91]

EP-A-0 494 615 (Beller et al.) - Discloses an echo contrast agent for ultrasound diagnosis comprising an aqueous preparation containing polyoxyethylene-polyoxypropylene polymers and negatively charged phospholipids for take-up and stabilization of microgas bubbles. [= AU 11547/92; U.S. 5,599,523]

WO 91/12823 (Illum L) - Discloses an ultrasonic contrast agent comprising gas-containing microcapsules with a plurality of gas filled voids, produced e.g. by the double emulsion method. The product is obtained in the form of a suspension which may be washed, sterilized, and used, or the microcapsules can be in some cases freeze-dried and stored as a free-flowing powder. The particles may also be used in nasal and lung delivery systems for drugs, and as opacifiers or reflectivity enhancers in cosmetics.

WO 92/18164 (Heath) - Discloses microcapsules, useful as diagnostic agents of blood and heart abnormalities - prepared by spray-drying a solution or dispersion of wall-forming material, e.g. albumin, gelatin, to obtain intermediate microcapsules then reducing their water-solubility.

WO 93/05819 (Quay) - Discloses a biocompatible contrast media for ultrasound imaging comprising an ultrasound image enhancing agent comprising a chemical which is a gas at the body temp. of an organism, having a Q coefficient greater than 5 where Q = 4 x 10 power (-7) x p/CsD (p is the density of the chemical as a gas (kg-3); Cs is the water solubility of the chemical as a gas (M); D is the diffusivity of the chemical as a gas in soln. (cm3sec-1)). The agent in the form of free gas microbubbles may be hexafluoropropylene, octafluoropropane, octafluorocyclobutane, n-pentane, isopentane, neopentane, cyclopentane, butane, cyclobutane, decafluorobutane, dodecafluoropentane, dodecafluoroneopentane, perfluorocyclopentane sulfur hexafluoride, hexafluoroethane, octafluoro-2-butene, hexafluoro-2-butyne, hexafluorobuta-1,3-diene or perfluorocyclobutane. The solution may also include a viscosity increasing agent, e.g. sorbitol.